The Promise of Metastasis-Directed Therapy for Oligometastatic Prostate Cancer: Going Beneath the Surface with Molecular Imaging

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Historically, metastatic disease was thought to represent an all-or-nothing incurable state, distinct from curable localized disease and necessitating treatment with systemic therapy alone. The role for life-prolonging local therapy was known to be futile. This dogma was challenged in the 1990s with the reframing of metastasis as a spectrum rather than binary, resulting in the postulation of a low-volume metastatic state, given the term *oligometastasis,* which may actually be curable with definitive local therapy.

WHAT IS THE CURRENT STATE OF OLIGOMETASTATIC PROSTATE CANCER?

Recently, randomized clinical trials across multiple disease sites (Table 1) (*1*–*5*) have demonstrated improvements in progression-free survival with the addition of metastasis-directed therapy (MDT) for oligometastatic disease, possibly due to ablation of subpopulations that would otherwise have led to subsequent dissemination or the nurturing of systemic microscopic disease toward macroscopic colonization. In line with this hypothesis, some of these randomized trials have demonstrated that local consolidation of macroscopic metastases delayed the time to development of new metastases and improved overall survival. Despite these early successes, key questions remain unanswered regarding the use of MDT in oligometastatic prostate cancer. How can we best identify patients likely to benefit from MDT? In the case of castration-sensitive prostate cancer, can we omit androgen deprivation therapy? What are the best MDT systemic therapy combinations?

The randomized clinical trials supporting the use of MDT adopted numeric definitions of oligometastasis (*6*). Within prostate cancer, a cutoff of no more than 3 metastases has been used frequently; however, additional definitions quantifying the volume of disease and incorporating metastasis location have also been explored. Although these definitions have proven useful, a radiographic numeric definition using conventional imaging alone is unlikely to capture the true extent of disease. For the foreseeable future, this principle will likely remain relevant to the study of oligometastatic disease, as any definition based on quantifying detectable lesions will always be contingent on the sensitivity and specificity of the detection method used. Analogous to an iceberg, what is detectable on imaging for MDT consolidation must best capture the extent of disease "above the surface" and minimize the potential for significant disease burden "beneath the surface" (*7*). The inaccuracies with older staging studies in identifying what was actually beneath the surface likely contributed greatly to the failures of previous attempts to show benefits of MDT in patients with metastasis. Thus, revisiting the impact of imaging on oligometastatic prostate cancer is timely, given the rapid adoption of exquisitely sensitive prostate-specific membrane antigen (PSMA) PET/CT imaging worldwide.

STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) AND MOLECULAR IMAGING ARE POTENTIALLY A POWERFUL COMBINATION FOR CURE OF OLIGOMETASTATIC PROSTATE CANCER

MDT entails direct local consolidative treatment of metastatic lesions and is commonly achieved through surgical metastasectomy or nodal dissection; thermal or chemical ablation; or the high-dose-per-fraction, precisely targeted radiotherapy known as SABR. Although for many metastatic lesions any of these local approaches would be reasonable as MDT, the noninvasive nature of SABR, the ease with which adjacent at-risk normal tissues can be spared, and the excellent tolerance in even the most medically comorbid has tipped the scales in favor of SABR as the MDT modality of choice. SABR may be even more effective for prostate cancer than for other histologies because of the radiobiologic characteristics of prostate cancer (α/β ratio of 0.5–2) (*8*), leading to a widened therapeutic window and offering greater efficacy at a higher dose per fraction and shorter total treatment times.

Although SABR represents an attractive MDT option for metastatic prostate cancer, MDT efficacy will always be dependent on identifying men with oligometastatic disease or with very little beneath the surface. The excellent sensitivity and specificity of

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TABLE 1
Randomized Clinical Trials Demonstrating Improvements in Progression-Free Survival with the Addition of Metastasis-Directed Therapy

Author	Disease site	Timing of oligometastasis	Oligometastatic definition	Sample size	Therapy	Primary endpoint
Iyengar et al. (*1*)	NSCLC	Synchronous	≤6 metastases (including primary)	29	SABR to all sites of disease followed by maintenance chemotherapy vs. maintenance chemotherapy	Median PFS, 9.7 vs. 3.5 mo favoring SABR
Gomez et al. (*2*)	NSCLC	Synchronous	≤3 metastases (not including primary)	49	LCT (surgery or RT) to all sites of disease followed by maintenance chemotherapy vs. maintenance chemotherapy	Median PFS, 14.2 vs. 4.4 mo favoring LCT
Phillips et al. (*3*)	CSPC	Metachronous	≤3 metastases	54	SABR to all sites of disease vs. observation	6-mo disease progression, 19% vs. 61% favoring SABR
Ost et al. (*4*)	CSPC	Metachronous	≤3 metastases	62	MDT (surgery or RT) to all sites of disease vs. observation	Median ADT-free survival, 21 vs. 13 mo favoring MDT
Palma et al. (*5*)	Varied histology	Metachronous	≤5 metastases	99	Standard of care + SABR vs. standard of care alone	5-y OS, 42.3% vs. 17.35 favoring SABR
EORTC 40004 (*15*)	Colorectal	Metachronous	<10 metastases	119	Standard of care + LCT vs. standard of care alone	Median OS, 45.6 mo vs. 40.5 mo favoring LCT

NSCLC = non–small cell lung cancer; PFS = progression-free survival; LCT = local consolidative therapy; RT = radiation therapy; CSPC = castration-sensitive prostate cancer; ADT = androgen deprivation therapy; OS = overall survival.

molecular imaging in prostate cancer provides an exciting opportunity to address the limitations of conventional imaging in assessing patients with presumed oligometastatic disease (*9*). This theoretic improvement should allow for both better patient selection and improved total MDT consolidation. The impact of identifying correct candidates for SABR MDT using more accurate molecular imaging was illustrated by our phase II Baltimore ORIOLE trial. We randomized 54 men with no more than 3 metastases on conventional imaging to observation or SABR. Men underwent masked PSMA PET/CT at baseline and 6 mo after treatment, resulting in 44.4% of these men having radiotracer-avid metastatic disease that was not identified on conventional imaging (i.e., disease beneath the surface). Incomplete MDT consolidation (untreated PSMA PET–avid disease) was associated with significantly worse distant progression at 6 mo (62.5% vs. 15.8%) (*3*). These findings reinforce how clinical staging with conventional imaging remains a major limitation to the success of MDT in oligometastatic disease and have translated into several series evaluating promising outcomes of molecular imaging–guided MDT in prostate cancer. PSMA PET–directed SABR has recently been explored in both castration-sensitive and castration-resistant oligometastatic disease (*10–12*). Two reports have also compared MDT using either PSMA PET or choline PET to identify metastatic lesions. Improvement in androgen deprivation therapy–free survival with PSMA-guided treatment (*13,14*) was observed as expected on the basis of the superiority of PSMA over choline for detecting disease beneath the surface.

THE FUTURE FOR MOLECULAR IMAGING IN THE MANAGEMENT OF OLIGOMETASTATIC PROSTATE CANCER IS BRIGHT

The identification of metastasis-free survival as a useful surrogate for overall survival in prostate cancer has had major implications for expediting discovery in a disease for which improvements in life expectancy and a plethora of salvage options have made overall survival endpoints increasingly difficult and time-consuming to meet. In a similar vein, molecular imaging as a biomarker, such as with PSMA PET, could function in a variety of ways beyond the identification of patients with oligometastatic disease: first, as a predictive biomarker capable of noninvasively distinguishing between patients likely to benefit from MDT and those best served by systemic therapy; second, as a prognostic, or treatment agnostic, readout that could be valuable for shared decision making and future design of future prospective trials; or third, as a biomarker for response to therapy. Our international collaborative effort is evaluating PSMA PET avidity changes after SABR MDT in oligometastatic prostate cancer and suggests that early PSMA PET response can be used to

predict lesion local failure and even metastasis-free survival (Philip Sutera et al., oral communication, December 2021). Efforts such as these will be critically important for defining the future roles and limitations of molecular imaging in guiding treatment of oligometastatic prostate cancer with SABR MDT. By no means will molecular imaging approaches be the only technique directing management of MDT in oligometastatic prostate cancer. Combinations of imaging biomarkers, liquid biopsy approaches (e.g., circulating tumor cells, cell-free DNA, or exosomes), and traditional patient-level clinical data will likely be the best solution. Finally, whereas both surgery and radiotherapy can provide excellent local control of metastatic deposits, management for oligometastatic disease resulting in cure will require achieving functional, if not literal, total consolidation of disease. Working toward this end will necessitate MDT strategies that prevent or delay subsequent progression of residual micrometastatic disease, either with MDT alone or more likely in combination with systemic agents (e.g., cytotoxic chemotherapy, targeted inhibitors, immunotherapy, or radiopharmaceuticals). Thus, we are optimistic that we will soon have precision medicine–guided approaches to enhancing the care for men with oligometastatic prostate cancer.

DISCLOSURE

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